Aventis Pasteur

April 2, 2004

IMOVAX® RABIES, RABIES VACCINE (HUMAN DIPLOID CELL)
PRODUCT RECALL
Medical Opinion from Aventis Pasteur Regarding Management of Patients

A recent Quality Assurance test of Imovax Rabies Vaccine revealed the presence of non-inactivated Pitman-Moore virus (the attenuated vaccine strain) in a single product lot. Imovax Rabies Vaccine is an inactivated viral vaccine and should not contain live virus. This above-mentioned lot was not distributed. As a precautionary measure, Aventis Pasteur has decided to initiate a voluntary recall of lots X0667-2, X0667-3, W1419-2, and W1419-3 which were produced during the same time period as the above-mentioned lot that contained non-inactivated Pitman-Moore virus. These four lots, which were distributed in the U.S. from September 23, 2003 through April 2, 2004, passed all release tests, including testing to confirm the absence of live virus, and no unusual pattern of adverse events has been noted for these lots by Aventis Pasteur, the Food and Drug Administration, or the Centers for Disease Control and Prevention.

We consider it appropriate to recall all lots produced during the relevant time period as a matter of company policy. Following the recommendations below will assure negligible risk to persons who have received vaccine from a recalled lot. The following outlines relevant medical information:

1. Prior to release to the marketplace, lots X0667-2, X0667-3, W1419-2, and W1419-3 underwent the standard release testing required by U.S. and European regulatory authorities, including injection of the vaccine into animals to verify safety and potency. All lots released for use passed all tests.

2. The manufacturing process does not use a wild rabies virus, but rather the attenuated Pitman-Moore vaccine production virus.

3. Vaccination with Imovax Rabies Vaccine in accordance with accepted postexposure prophylaxis schedules rapidly produces sufficient antibody to neutralize live rabies virus. This has been evidenced through clinical trials and by the product's success in protecting people who have suffered bites from rabies-infected animals.

We believe it to be highly unlikely that use of vaccine from the lots being recalled would pose any risk to recipients. We nonetheless recommend that patients and physicians take the additional steps outlined below to provide further assurance. (Please see the enclosed *Instructions for Complying with Recall* for information regarding Aventis Pasteur's support for expenses incurred while following these recommendations.)

RECOMMENDATIONS FOR PERSONS RECEIVING RECALLED RABIES VACCINE

Most persons receiving rabies vaccine do so because of exposure to a rabid animal, and treatment is needed to prevent fatal illness. Thus, it is extremely important that persons receiving postexposure prophylaxis not omit or delay any remaining injections; the remaining injections should be administered using non-recalled vaccine. Recalled vaccine is considered fully immunogenic, and previously administered doses can be considered a dose in a postexposure prophylaxis regimen.

There remains a theoretical possibility that persons who received a recalled lot of vaccine could have been exposed to the non-inactivated Pitman-Moore strain of rabies virus. Thus, patients who received recalled vaccine should receive treatment equivalent to postexposure prophylaxis, similar to published guidelines, as follows:
(http://www.cdc.gov/ncidod/dvrd/rabies/professional/publications/ACIP/ACIP99.pdf)

Persons who were immunized with recalled vaccine as part of a course of postexposure prophylaxis for a possible rabies exposure

- **Not Previously Immune (persons who had not received at least 3 doses of vaccine at some time prior to the possible rabies exposure):** persons without prior immunity who have a possible rabies exposure routinely receive a 5-dose postexposure immunization series. If this postexposure series has not already been completed, such persons should complete the full postexposure series, *using non-recalled vaccine to complete the series.* It is not necessary to repeat doses that already have been given as part of the 5-dose series, even if recalled vaccine was used. In addition, if RIG* (rabies immune globulin) was not given with the first dose of vaccine *and* it has been < 7 days since the first dose of vaccine, RIG should be administered at this time. Once postexposure prophylaxis is completed, persons are considered protected against both the original rabies exposure and any possible exposure to non-inactivated virus in the recalled vaccine.

- **Previously Immune (persons who had received at least 3 doses of vaccine at some time prior to the possible rabies exposure):** persons with pre-existing immunity (i.e., have previously completed a full preexposure or postexposure vaccination series) who then have a possible rabies exposure routinely receive 2 booster doses of rabies vaccine. If one or both doses already were given using recalled vaccine, they should receive 2 more doses *using non-recalled vaccine*. RIG is not recommended.

Persons who were immunized with recalled vaccine for reasons other than a possible rabies exposure

- **Not Previously Immune (persons who had not received at least 3 doses of vaccine at some previous time):** persons without prior immunity who received recalled vaccine as part of a 3-dose preexposure vaccination series should receive additional doses *using non-recalled vaccine* for a total of 5 doses (dosing intervals should follow the post- exposure prophylaxis schedule as closely as possible). RIG* is recommended if it has been < 7 days since administration of the first dose of vaccine.

- **Previously Immune (persons who had received at least 3 doses of vaccine at some previous time):** persons with pre-existing immunity (i.e., completed a full preexposure or postexposure vaccination series before they received recalled vaccine) who received recalled vaccine as a routine booster dose should receive two additional doses of *non-recalled vaccine*. RIG is not recommended.

For clarification of the above recommendations, please contact Aventis Pasteur Medical Information Services Department at 1-800-835-3587.

This Medical Opinion was prepared with concurrence of the U.S. Food and Drug Administration and the U.S. Centers for Disease Control and Prevention.

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*Where available (including U.S.), Human Rabies Immune Globulin (HRIG) is preferred and is administered in a dose of 20 IU/kg. Where HRIG is not available, Equine Rabies Immune Globulin may be used in a dose of 40 IU/kg. These dosages are applicable for all age groups, including children. For persons receiving RIG after having received recalled vaccine administered as part of postexposure prophylaxis, as much of the dose as is anatomically feasible should be infiltrated at the site of the original rabies exposure (e.g., a wound), and as much of the remaining dose as is anatomically feasible should be infiltrated at the site(s) where the recalled vaccine was injected. If any RIG remains, it should be administered intramuscularly at an anatomically distant site. Persons receiving RIG for recalled vaccine given as part of a preexposure vaccination series should have as much of the dose as is anatomically feasible infiltrated at the site(s) where recalled vaccine was given, and the rest should be administered intramuscularly at an anatomically distant site. RIG should never be administered in the same syringe as vaccine, or into the same anatomical site used for concomitant vaccination. Because RIG may partially suppress active production of antibody, no more than the recommended dose should be given.